REMARKS

Statement of Substance of Interview

As an initial matter, counsel would like to thank Examiner Rodriguez-Garcia and Examiner Saeed for the courtesies extended during the telephone interview conducted October 28, 2009.

During the interview, the Examiners advised that the claim amendments presented herein should be able to overcome all the objections and rejections in the Office Action of July 28, 2009.

Response to Office Action of July 28, 2009

In the present Amendment, the title has been amended according to the Examiner's suggestion. Claim 1 has been amended to further characterize formula (I). Section 112 support for the amendment to ring A is found, for example, at page 10, lines 20-25 of the specification. Claims 2-3 and 6-11 have been cancelled without prejudice or disclaimer. Claims 4 and 5 have been amended to improve their form. New claims 12-15 have been added. Section 112 support for claim 12 is found, for example, at page 10, lines 25-26 of the specification. Section 112 support for claims 13-15 is found, for example, in the Examples of the specification. No new matter has been added, and entry of the Amendment is respectfully requested.

Upon entry of the Amendment, claims 1, 4-5 and 12-15 will be pending.

Response to § 112 Rejection

At page 3 of the Action, claims 1-11 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite.

The claims have been amended to address the Examiner's concerns. Specifically, brackets and parentheses have been deleted, claim 1 no longer recites the proviso, the claims no

longer recite pharmaceutical salts of pharmaceutical salts, and claims 5 and 8 recite "a" compound instead of "at least one" compound. Accordingly, withdrawal of the § 112 rejection is requested.

Response to Double Patenting Rejections

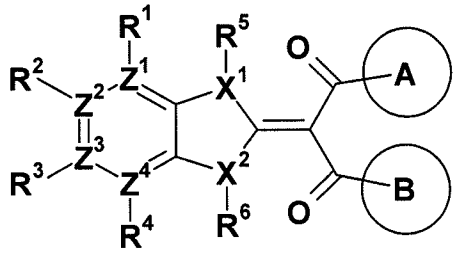
At page 4 of the Action, claims 1-11 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-2 of U.S. Patent No. 6,960,591.

At page 5 of the Action, claims 1-11 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentabie over claims 1-3 of U.S. Patent No. 7,569,688.

Applicant submits that the above two double patenting rejections should be withdrawn because the present claims are not obvious over claims 1-2 of the '591 patent or claims 1-3 of the '688 patent.

The '688 patent is a divisional of the '591 patent.

The compound recited in claim 1 of the '688 patent and the '591 patent is represented by the general formula (I):

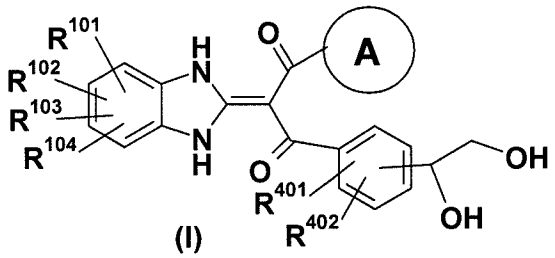


Formula (I) of the '591 and '688 patents

wherein ring A and ring B are the same or different and are each an aryl which may be substituted or a heterocycle which may be substituted.

The substituents on the aryl or heterocyclic group represented by ring A and ring B are chosen from, but do not necessarily include all of, (1) CN, (2) NO_2, (3) halo, (4) OH, (5) COOH, (6) C_{1-10} alkyl-T^{104}- which may be substituted by (OH, halo, heterocyclic group, C_{6-14} aryl which may be substituted by Halo, $R^{101}R^{103}N$, R^{101}-CO-, R^{101}-T^{101}-CO- or R^{101}-T^{101}-), wherein T^{104} is a bond, -O-, -COO-, or -OCO-, (7) acyl which may be substituted by R^{113}, (8) acyl-O- which may be substituted by R^{113}, (9) $R^{116}R^{117}N$, (10) $R^{116}R^{117}NCO$. See, col. 9, lines 54-56 and col. 12, lines 10-23 of the '591 patent.

In contrast, present claim 1 as amended relates to a propane-1,3-dione derivative represented by the following formula (I):

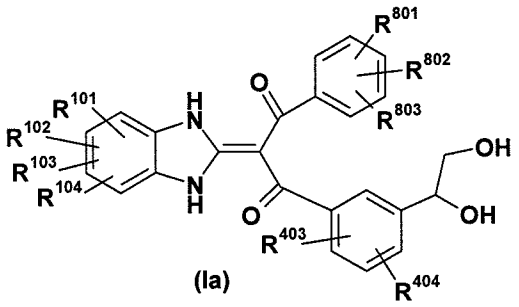


(I)

Formula (I) of Present Claims

wherein ring A is benzene which may be substituted with 1 to 3 substituent groups, wherein the substituent group is halogen, CN, lower alkyl which may be substituted with halogen, -O-lower alkyl, -CO-O-lower alkyl or amino; R^{401} and R^{402} may be the same or different from each other and each is H, halogen, OH, -O-lower alkyl, or lower alkyl.

Further, independent claim 4 recites a propane-1,3-dione derivative represented by the following formula (Ia):



(Ia)

Formula (Ia) of Present Claims

wherein R^{801}, R^{802} and R^{803} may be the same or different from one another and each is H, halogen or lower alkyl; and R^{403} and R^{404}: may be the same or different from each other and each is H, halogen or lower alkyl.

It has been established that it remains necessary to identify some reason that would have led a chemist to modify a known compound in a particular manner to establish prima facie obviousness of a new claimed compound and that prior art would have suggested making the specific molecular modifications necessary to achieve the claimed invention. See, *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350 (Fed. Cir. 2007) and *Eisai Co. Ltd. v. Dr. Reddy's Labs., Ltd.*, 533 F.3d 1353 (Fed. Cir. 2008).

However, there are many variations with respect to the substituents R^1, R^2, R^3, R^4, ring A and ring B in the general formula (I) of the '591 and '688 patents. One skilled in the art would understand that there is a huge number of compounds based on the combinations of these substituents. Further, the claims of the '591 and '688 patents do not recite specific substituents on ring A and ring B, much less the specific substituent 1,2-dihydroxyethyl on ring B as required by present claim 1. As indicated above, even the specific substituents listed in the disclosures of the '591 and '688 patents do not include the claimed substituent 1,2-dihydroxyethyl on ring B.

Further, an object of the invention of the '688 and '591 patents is to obtain a non-peptide compound having GnRH receptor-antagonizing activity.

In contrast, an technical feature of the present invention is a medicament, particularly, a novel propane-1,3-dione derivative which is useful for treating sex hormone dependent diseases.

As the technical background at the time the present invention was made, it was known that certain propane-1,3-dione derivatives have an GnRH receptor antagonizing activity, as disclosed in the paragraph bridging pages 3 and 4 of the specification.

However, the present inventors conducted extensive studies with an object to obtain a compound which not only has an excellent GnRH receptor antagonizing activity but also has excellent distribution to blood and excellent metabolism stability, and shows low drug interaction. It is well known in the medicinal chemistry field that even if a compound has an excellent *in vitro* activity, it does not necessarily maintain the activity *in vivo*. Therefore, even if a compound having a benzimidazol-2-ilidene-1,3-diphenyl-1,3-dione structure is known to show *in vitro* GnRH receptor antagonizing activity, it does not necessarily maintain the activity *in vivo*. For the development of pharmaceuticals, the *in vivo* pharmacological effects are essential for research. Moreover, in order to make a medicament, factors other than pharmacological activity need to be taken into consideration, e.g., whether the compound has good distribution to the blood by oral administration, whether the compound has good stability after entering the blood, and whether the drug-drug interaction (DDI) of the compound is appropriate in view of the object of the invention.

Pharmaceutical companies aim to obtain compounds which have excellent pharmacological activity, have good ADME (absorption, distribution, metabolism and excretion)

and have improved *in vivo* pharmacological activity in order to meet a strict requirement for getting approval from FDA. These goals have been achieved by the present invention.

Having conducted extensive studies, the present inventors have found, unexpectedly, that the 2-(1,3-dihydro-2H-benzimidazol-2-ylidene)propane-1,3-dione compound represented by the formulas (I) and (Ia), wherein the ring A and ring B are benzene rings and 1-hydroxyalkyl (particularly, 1,2-dihydroxyethyl) is substituted on the ring B, has excellent properties. That is, the presently claimed compound not only has an excellent GnRH receptor antagonizing activity, but also has excellent distribution to the blood by oral administration, has excellent metabolic stability, and has less drug-drug interaction. Thus, the present inventors not only discovered a compound having an excellent GnRH receptor antagonizing activity but also took the effectiveness *in vivo* into consideration.

The '591 and '688 patents do not provide any teaching, suggestion or motivation to one skilled in the art to select 1,2-dihydroxyethyl for the purpose of achieving such goals.

Still further, the present invention provides unexpectedly superior results in comparison to the compounds in the '591 and '688 patents.

Specifically, Applicants employed Examples 40, 251 and 239 in Patent Reference 1, WO 02/02533, which is the corresponding PCT publication of the '591 and '688 patents, as Control Compounds 1-3, respectively, in the examples of the specification. See, Table 25 at page 89 of the specification.

As disclosed at page 89, line 10 to page 90, line 2 of the specification, a compound having a larger ratio of blood drug concentration to in vitro receptor inhibitory activity has a stronger drug effect in the living body. As shown by the data in Table 25, the presently claimed

compounds have higher ratios of blood concentration to receptor inhibitory activity [(B)/(A)] in comparison to Control Compounds 1-3. This indicates that the presently claimed compounds have a stronger drug effect than Control Compounds 1-3.

Also, the presently claimed compounds have superior metabolic stability in human liver and are less likely to suffer from the first pass effect in comparison with Control Compounds 1-3. See, the paragraph bridging pages 93-94 of the specification.

Additionally, as shown by the data in Table 26 at page 92 of the specification, the compound of the present invention has a lower inhibition of CYP3A4 inhibitory activity and thus it is believed that the compound of the present invention has a low risk of drug-drug interaction with the drugs that affect CYP3A4 activity.

As explained above, the compound of the present invention has excellent properties, i.e., excellent blood distribution via oral administration, excellent metabolic stability, and lower drug-drug interaction in addition to excellent GnRH receptor antagonizing activity.

The '591 and '688 patents do not teach or suggest the presently claimed compounds and the unexpectedly superior results provided by the claimed compounds.

In view of the above, the present claims are not obvious over the claims of the '591 and '688 patents. Reconsideration and withdrawal of the double patenting rejections are respectfully requested.

Response to Claim Objections

At page 5 of the Action, claim 1 is objected to for containing two "(I)" symbols in the claim. Claims 1, 4, 6 and 9 recite "by the general formula", however, per the Examiner, there are formulae (I), (Ia) and (Ib), and these are not general, because all the variables are defined.

Claim 1 has been amended to delete the extra "(I)" symbol. Claims 1-4 have been amended to recite "by the formula" and claims 6-9 have been cancelled. Accordingly, withdrawal of the objections to the claims is requested.

Title

At page 6 of the Action, a new title is required that is clearly indicative of the invention to which the claims are directed. The Examiner suggests including in the title the name of the main core of the chemical structure (e.g., benzimidazolidine propane-1,3-dione) and the utility possessed by the compounds which Applicants regard as their invention.

As noted, the title has been amended according to the Examiner's suggestion.

Allowance is respectfully requested. If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

The USPTO is directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

Respectfully submitted,

Hui Chen Wauters

Hui C. Wauters
Registration No. 57,426

SUGHRUE MION, PLLC
Telephone: (202) 293-7060
Facsimile: (202) 293-7860
WASHINGTON DC SUGHRUE/265550
65565
CUSTOMER NUMBER

Date: October 28, 2009